REMARKS/ARGUMENTS:

Claims 1, 3-8, 10-15, 17-19, 21, and 22 are pending in the application. Reexamination and reconsideration of the application, in view of the following remarks, are respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C § 112:

Claims 1, 3-8, 10-15, 17-19, 21, and 22 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Specifically, the Examiner states that the claims fail to be enabled for *in vivo* applications. The Applicant respectfully traverses this rejection.

The Applicant's specification at page 14, lines 1-20 teaches how cancer cells may be contacted with one or more glucosylceramide synthase antisense compounds either *in vitro* or *in vivo*. In addition, at page 15, line 28-page 16, line 9 of the Applicant's specification methods of reversing drug resistance in a cancer cell or inducing apoptosis in a caner cell in a subject by administering glucosylceramide synthase antisense compounds are described. Consequently, the present invention is enabled for *in vivo* applications. Furthermore, *in vitro/in vivo* models should be accepted as correlating unless the Examiner has evidence that the model does not correlate.

> "In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)" MPEP 2164.02

In view of the foregoing, Applicant respectfully submits that the specification provides sufficient support for methods for reversing drug resistance or inducing apoptosis in cancer cells by introducing an antisense glucosylceramide synthase nucleic acid sequence into cancer cells and formulations comprising an antisense glucosylceramide synthase nucleic acid sequence and a chemosensitizer or chemotherapeutic agent. Withdrawal of this rejection is thus respectfully requested.

CLAIM REJECTIONS UNDER 35 U.S.C § 103:

Claims 1, 3-8, 10-15, 17-19, 21, and 22 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ichikawa et al. in view of Milner et al., the combination in view of Liu et al. and Lucci et al.

Claim 1 is as follows:

> A method for reversing drug resistance in a cancer cell, said method comprising introducing an antisense glucosylceramide synthase nucleic acid sequence into said cell, wherein said introduction reverses drug resistance in said cell.

Applicant respectfully submits that the cited references cannot render claim 1 obvious, because the cited references fail to teach or suggest introducing an antisense glucosylceramide synthase nucleic acid sequence into a cell, wherein the introduction reverses drug resistance in the cell.

Ichikawa teaches the cloning of the cDNA sequence for human GCS. Ichikawa fails to teach or suggest the use of an **antisense glucosylceramide synthase** nucleic acid sequence to reverse drug resistance.

Milner provides a **general review** on antisense technology. However, Milner **fails to teach or suggest** the use of an **antisense glucosylceramide synthase** nucleic acid sequence to reverse drug resistance.

Lucci teaches the correlation between increases in glucosylceramide levels and the induction of apoptosis in drug resistant target cells *in vitro*. Lucci has **no teaching or suggestion** whatsoever **of using antisense** glucosylceramide synthase nucleic acid sequences for any purpose much less for reversing drug resistance.

Liu teaches the expression of glucosylceramide synthase and the resulting increase in drug resistance of target cells. However, there is **no teaching or suggestion of using antisense** glucosylceramide synthase nucleic acid sequences for reversing drug resistance. Furthermore, since Liu teaches that cellular resistance and GCS activity were dependent upon the concentration of the expression mediator doxycycline, there would be no motivation to switch to using antisense glucosylceramide synthase nucleic acid sequences for regulating drug resistance.

In light of the foregoing, Applicant respectfully submits that the cited references could not have made claim 1 obvious, because the cited references fail to teach or suggest each and every claim limitation. Claims 3-7 depend from claim 1 and cannot be made obvious for at least the same reasons as claim 1. Claims 8, 10-15, 17-19, 21, and 22, although not depending from claim 1, require the presence of an antisense glucosylceramide synthase nucleic acid sequence in a cell for the purpose of either reversing drug resistance or inducing apoptosis or both. Therefore, claims 8, 10-15, 17-19, 21, and 22 cannot be rendered upatentable over the cited references for the same reasons discussed above. Withdrawal of these rejections is thus respectfully requested.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: August 12, 2004

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